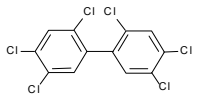
2,2',4,4',5,5'-hexachlorobiphenyl (PCB153)



Rationale for study

- Human exposure
  - Most prevalent di-ortho PCB congener
- Potential interactions with dioxin-like congeners
- Part of mixture study with PCB126

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Study Design: PCB153

- Female Sprague-Dawley rat only
- Oral gavage: 5 days per week
- Vehicle: corn oil:acetone (99:1) - 2.5 ml/kg
- Time points: 14-, 31-, 53- week and 2-year
- Doses
  - 10, 100, 300, 1000, and 3000 ug/kg
  - 3000ug/kg stop exposure
  - Doses not based on relationship to MTD
  - Chosen to match doses used in mixture study of PCB126:153

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PCB153 study design in context

PCB153 (ug/kg)	PCB 126 (ng/kg)				
	0	10	100	300	1000
0	Multiple	TR520	TR520	TR520	TR520
10	TR529	TR530			
100	TR529		TR530	TR530	
300	TR529			TR530	
1000	TR529				TR530
3000	TR529			TR530	

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Survival and body weight

- No effect on survival
- Effect on body weight gain
  - No effect at 14, 31 or 53 weeks.
  - Reduced in 3000ug/kg group
    - <95% controls after week 69 of study

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Distribution of PCB153

- Dose and duration of exposure dependent increases
  - Measurable levels in fat, liver, lung and blood
  - Fat-main distribution site
- PCB153 detectable in rodent chow
  - 92 pg/g feed median value (34-5140 range)
  - Approx 5 ng/kg/day intake (2000x lower than lowest dose used)
- Measurable levels in fat of controls
  - 436 ng/g at 2 years average level
  - 46 fold lower than level in fat of lowest dose group at 2 years

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Biochemical effects

- Increased cytochromes P450 activity
  - Liver PROD increased at all doses 100 ug/kg and higher at all times
    - 40-140 fold increase at highest dose
  - Weak effect on liver EROD and ACOH
    - < 2 fold increase
    - No effect at 53 weeks
  - Lung EROD
    - Decreased at 14 weeks at 300 ug/kg and greater
- Modest alterations in thyroid hormones
  - Decreased free and total T4 at highest dose at 14 and 53 weeks only
  - T3 decreased only at 14 weeks at highest dose
  - No effect on TSH

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Liver: 2 year

	0	10	100	300	1000	3000	Stop
Animals per group	53	54	53	53	53	51	50
Hepatocyte hypertrophy	0	5*	5*	24*	39*	41*	32*
Fatty change, diffuse	3	7	2	11*	21*	17*	15*
Bile duct hyperplasia	5	3	2	14*	10	17*	12*
Oval cell hyperplasia	0	0	0	1	0	4*	2
Pigmentation	1	1	2	5	5	9*	3
Cholangioma[a]	0	0	0	0	2	0	2

p<0.05; [a]Historical control incidence; 0/371

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Thyroid: 2 year

	0	10	100	300	1000	3000	Stop
Animals per group	51	52	53	53	53	51	49
Follicular cell hypertrophy	5	9	9	12*	10	17*	12*
Follicular cell adenoma[a]	0	0	0	0	0	0	2
C-cell adenoma/carcinoma	18*	15	18	13	23	7*	19

* P<0.05,
[a] Historical control range 1/367 (0.3%)

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Other organs: Non-neoplastic effects

- Ovary
  - Chronic active inflammation
- Oviduct
  - Chronic active inflammation
- Uterus
  - Inflammation, suppurative
  - Chronic active inflammation

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Conclusions-PCB153

- Equivocal evidence of carcinogenicity
- Based on
  - Cholangioma of the liver

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